```
FILE 'HOME' ENTERED AT 14:34:16 ON 03 DEC 2002

=> file medline, biosis, embase, scisearch, caplus
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                ENTRY       SESSION
FULL ESTIMATED COST                             0.42          0.42


FILE 'MEDLINE' ENTERED AT 14:35:17 ON 03 DEC 2002

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FILE 'CAPLUS' ENTERED AT 14:35:17 ON 03 DEC 2002
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=> s diabetes
L1       655376 DIABETES


=> s l1 and GIP promtoer
L2            0 L1 AND GIP PROMTOER

=> s l1 and GIP promoter
L3            6 L1 AND GIP PROMOTER

=> s l3 and insulin
L4            6 L3 AND INSULIN

=> s nucleic acid and insulin
L5         2777 NUCLEIC ACID AND INSULIN


=>

=> s l5 and GIP promoter
L6            0 L5 AND GIP PROMOTER

=> dup rem
ENTER L# LIST OR (END):l3
PROCESSING COMPLETED FOR L3
L7            2 DUP REM L3 (4 DUPLICATES REMOVED)

=> s l1 and secretagogue
L8          490 L1 AND SECRETAGOGUE

=> s l3 and GIP promoter
L9            6 L3 AND GIP PROMOTER

=> dup rem
ENTER L# LIST OR (END):l9
PROCESSING COMPLETED FOR L9
L10           2 DUP REM L9 (4 DUPLICATES REMOVED)
```

```
=> dup rem
ENTER L# LIST OR (END):l8
PROCESSING COMPLETED FOR L8
L11          226 DUP REM L8 (264 DUPLICATES REMOVED)

=> s l11 and py <= 2000
    2 FILES SEARCHED...
    4 FILES SEARCHED...
L12          179 L11 AND PY <= 2000

=> s l8 and insulin gene
L13            2 L8 AND INSULIN GENE
```

PASSWORD:
 * * * * * * RECONNECTED TO STN INTERNATIONAL * * * * * *
SESSION RESUMED IN FILE 'MEDLINE, BIOSIS, EMBASE, SCISEARCH, CAPLUS'
AT 15:19:01 ON 03 DEC 2002
FILE 'MEDLINE' ENTERED AT 15:19:01 ON 03 DEC 2002
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COST IN U.S. DOLLARS   SINCE FILE   TOTAL
                                                  ENTRY   SESSION
FULL ESTIMATED COST   58.20   58.62

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)   SINCE FILE   TOTAL
                                                  ENTRY   SESSION
CA SUBSCRIBER PRICE   -0.62   -0.62

=> s diabetes and gene therapy
L14   1726 DIABETES AND GENE THERAPY

=> s l14 and insulin gene
L15   210 L14 AND INSULIN GENE

=> dup rem
ENTER L# LIST OR (END):l15
PROCESSING COMPLETED FOR L15
L16   107 DUP REM L15 (103 DUPLICATES REMOVED)

=> s obesity
L17   213019 OBESITY

=> s l17 and gene therapy
L18   265 L17 AND GENE THERAPY

=> s l18 and leptin
L19   91 L18 AND LEPTIN

=> dup rem
ENTER L# LIST OR (END):l19
PROCESSING COMPLETED FOR L19
L20   64 DUP REM L19 (27 DUPLICATES REMOVED)

=> s l16 and py>= 1998
   3 FILES SEARCHED...
L21   70 L16 AND PY>= 1998

=> s l20 and py >= 1998
   4 FILES SEARCHED...
L22   58 L20 AND PY >= 1998

ACCESSION NUMBER: 2000:876306   CAPLUS
DOCUMENT NUMBER: 134:51673
TITLE: Glucose-dependent insulin release from genetically
                           engineered K cells
AUTHOR(S):   Cheung, Anthony T.; Dayanandan, Bama; Lewis, Jamie T.;
                           Korbutt, Gregory S.; Rajotte, Ray V.; Bryer-Ash,
                           Michael; Boylan, Michael O.; Wolfe, M. Michael;
                           Kieffer, Timothy J.
CORPORATE SOURCE: Departments of Medicine and Physiology, University of
                           Alberta, Edmonton, AB, T6G 2S2, Can.
SOURCE: Science (Washington, D. C.) (2000), 290(5498),
                           1958-1962
                           CODEN: SCIEAS; ISSN: 0036-8075
PUBLISHER: American Association for the Advancement of Science
DOCUMENT TYPE: Journal
LANGUAGE: English

AB   Genetic engineering of non-.beta.-cells to release insulin upon feeding
      could be a therapeutic modality for patients with **diabetes**. A
      tumor-derived K-cell line was induced to produce human insulin by
      providing the cells with the human insulin gene linked to the
      5'-regulatory region of the gene encoding glucose-dependent insulinotropic
      polypeptide (GIP). Mice expressing this transgene produced human insulin
      specifically in gut K cells. This insulin protected the mice from
      developing **diabetes** and maintained glucose tolerance after
      destruction of the native insulin-producing .beta.-cells.

REFERENCE COUNT: 24   THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS
                                  RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB   Successful beta-cell replacement therapy in insulin-dependent (type I)
      diabetes is hindered by the scarcity of human donor tissue and by
      the recurrence of autoimmune destruction of transplanted beta cells.
      Availability of non-beta cells, capable of releasing insulin and escaping
      autoimmune recognition, would therefore be important for **diabetes**
      cell therapy. We developed rat pituitary GH3 cells stably transfected with
      a furin-cleavable human proinsulin cDNA linked to the rat PRL promoter.
      Two clones (InsGH3/clone 1 and 7) were characterized in vitro with regard
      to basal and stimulated insulin release and proinsulin transgene
      expression. Mature insulin secretion was obtained in both clones,
      accounting for about 40% of total released (pro)insulin-like products.
      Immunocytochemistry of InsGH3 cells showed a cytoplasmic granular insulin
      staining that colocalized with secretogranin II (SGII) immunoreactivity.
      InsGH3 cells/clone 7 contained and released in vitro significantly more
      insulin than clone 1. **Secretagogue**-stimulated insulin secretion
      was observed in both InsGH3 clones either under static or dynamic
      conditions, indicating that insulin was targeted also to the regulated
      secretory pathway. Proinsulin mRNA levels were elevated in InsGH3 cells,
      being significantly higher than in betaTC3 cells. Moreover, proinsulin
      gene expression increased in response to various stimuli, thereby showing
      the regulation of the transfected gene at the transcriptional level. In
      conclusion, these data point to InsGH3 cells as a potential beta-cell
      surrogate even though additional engineering is required to instruct them
      to release insulin in response to physiologic stimulations.

AB   Using the Adeno-associated virus (AAV) as a gene delivery vehicle, we have
     constructed a recombinant vector containing the full length rat
     preproinsulin gene (vLP-1). Utilizing the well described non-obese
     diabetic (NOD) mouse model, an experimental group (n = 10) of animals were
     intramuscularly (i.m.) injected with 10(7) rAAV virions containing the
     insulin gene and compared to a mock-injected control
     group (n = 10). Blood glucose (glc) was then measured weekly for 16 weeks.
     Data showed that the experimental group contained 70% euglycemic animals
     (defined as glc<200 mg/dL) versus 10% of the control animals (P < .05) at
     14 weeks. Mean weight in the treated group was greater than the untreated
     group. Insulin mRNA was detected at the injection site of all of the
     treated animals, but not controls. Complete destruction of islets was
     confirmed by histology ruling out the possibility of spontaneous reversal
     of insulinitis. We conclude that i.m. delivery of the **insulin
     gene** in the NOD mouse was able to prevent clinical DM up to 14
     weeks in a majority of treated animals. Our experimental data suggests
     that **gene therapy** may be an alternative treatment for
     IDDM in the future.

AB   PURPOSE: The objective of this study was to examine glucose modulated
      reporter gene expression via recombinant adeno associated viral vectors
      both in vitro and in vivo. METHODS: Huh7 human hepatoma cells were
      transduced by recombi nant adeno-associated virus (rAAV) vectors
      containing the luciferase gene under control of the rat insulin I gene
      promoter and a cytomegalovirus immediate-early promoter driving-enhanced
      green fluores cence protein gene. The reporter gene expression was
      evaluated by glucose stimulation either in the absence or presence of
      insulin se cretagogues, including phorbol-12-myristate-13-acetate,
      dibutyryl cy clic AMP, and forskolin. In vivo studies were performed by
      injecting rAAV into the livers of streptozotocin-induced diabetic C57BL/6J
      mice followed by measurements of blood glucose concentration and
      luciferase activity assays 2 weeks after rAAV injection. RESULTS: At a
      multiplicity of infection of 500, approximately 66-69% of cells expressed
      enhanced green fluorescence protein at 48 h post transduction. Luciferase
      activities, driven by the **insulin gene** promoter, in
      the rAAV-transduced hepatoma cells responded to milli molars of glucose.
      The addition of phorbol-12-myristate-13-acetate dibutyryl cyclic AMP, and
      forskolin increased luciferase expression in the presence of either 1 mM
      or 25 mM glucose. The stimulation of luciferase activities by these
      substances was inhibited by the presence of 100 nM staurosporine. Exposure
      to increments of exogenous in sulin up to 10(-7) M inhibited luciferase
      gene expression in rAAV transduced Huh7 cells. The in vivo experiments
      demonstrated good correlation between luciferase activities and blood
      glucose levels in streptozotocin-induced diabetic animals. CONCLUSION:
      rAAV is a promising vector for hepatic **gene therapy**
      for **diabetes**. Glucose and insulin secretagogues modulated
      transgene ex pression in rAAV-transduced hepatoma cells, suggesting that
      condi tions affecting **insulin gene** promoter function
      in pancreatic islet beta cells also affect transgene expression in human
      hepatoma cells con ferred with **insulin gene** promoter.
      Results obtained from in viv experiments demonstrated that glucose
      modulated transgene expres sion can be obtained in rAAV-treated diabetic
      C57BL16J mice.

AB   Type 1 **diabetes** results from the loss of insulin-producing
      pancreatic beta cells following the action of beta-cell-specific
      autoimmune responses. One possible treatment for type 1 **diabetes**
      is the development of beta-cell substitutes by introducing an
      insulin-producing gene into non-beta cells, which would evade the
      beta-cell-specific autoimmune attack. However, this approach has been
      hampered by the absence of (1) an appropriate glucose-sensing system to
      regulate **insulin gene** transcription; (2) enzymes that
      process proinsulin to insulin; and (3) glucose-regulatable exocytosis in
      the target cells. Recent attempts to solve these problems have sought new
      methods for effective gene transfer and have addressed issues such as the
      expression and release of insulin in response to the physiological
      stimulus of glucose, the production of biologically active insulin, and
      the selection of an ideal target cell for the expression of the
      insulin gene.

ACCESSION NUMBER: 2001383235   MEDLINE
DOCUMENT NUMBER: 21193101   PubMed ID: 11295563
TITLE: K cells: a novel target for **insulin gene
                       therapy** for the prevention of **diabetes**.
AUTHOR: Corbett J A
CORPORATE SOURCE: The Edward A. Doisy Dept of Biochemistry and Molecular
                       Biology, St Louis University School of Medicine, 1402 South
                       Grand Blvd, St Louis, MO 63104, USA.. corbettj@slu.edu
SOURCE: TRENDS IN ENDOCRINOLOGY AND METABOLISM, **(2001
                       May-Jun)** 12 (4) 140-2. Ref: 20
                       Journal code: 9001516. ISSN: 1043-2760.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
                       General Review; (REVIEW)
                       (REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010709
                       Last Updated on STN: 20010709
                       Entered Medline: 20010705

AB   Recently, gut K cells have been shown to express glucokinase, the glucose
     sensor of pancreatic beta cells, and transgenic mice expressing human
     insulin under the control of a K cell-specific promoter are resistant to
     diabetes development induced by the beta-cell toxin
     streptozotocin. These novel findings suggest that gut K cells might be a
     suitable target for gene therapeutic treatment of type 1 **diabetes**
     mellitus.

TITLE: Regulated hepatic **insulin gene
                       therapy** of STZ-diabetic rats.
AUTHOR: Thule P M; Liu J M
CORPORATE SOURCE: Department of Medicine, Emory University School of
                       Medicine, and Atlanta VA Medical Center, GA 30033, USA.

AB   Effective and safe **insulin gene therapy** will
       require regulation of transgenic insulin secretion. We have created a
       liver-targeted insulin transgene by engineering glucose responsive
       elements into a hepatic promoter containing an inhibitory insulin response
       sequence. In this work, we demonstrate application of this transgene for
       the treatment of **diabetes** mellitus in vivo, by administering a
       recombinant adenovirus vector, Ad/(GIRE)3BP-1 2xfur, to rats made diabetic
       with streptozotocin. We verified hepatic expression of transgenic insulin
       by RT-PCR, and confirmed glucose responsive stimulation of transgenic
       insulin secretion in vivo by serum RIA. Following a portal system
       injection of either Ad/(GIRE)3BP-1 2xfur, or an empty adenoviral vector,
       animals made diabetic with either low (120 mg/kg), or high (290 mg/kg)
       dose streptozotocin (STZ) were monitored for changes in body weight, and
       blood glucose. Without subcutaneous insulin injections, blood glucose
       values of sham-treated animals (n = 8) remained elevated, and animals
       failed to gain weight (n = 4), or died (n = 4). In contrast, body weight
       of Ad/(GIRE)3BP-1 2xfur-treated animals (n = 13) increased, and blood
       glucose remained at near normal levels from one to 12 weeks. Glucose
       values <50 mg/dl were infrequently observed, and no Ad/(GIRE)3BP-1
       2xfur-treated animal succumbed to hypoglycemia. Treatment with the insulin
       transgene enabled diabetic animals to reduce blood sugars following a
       glucose load, and to maintain blood sugar levels during a 10-h fast.
       Hepatic production of human insulin produced near normal glycemia, and
       weight gain, without exogenous insulin, and without lethal hypoglycemia.
       In conclusion, we have demonstrated the feasibility of utilizing
       transcription to control transgenic insulin production in a rodent model
       of **diabetes** mellitus

TITLE: Present and potential future use of **gene
                        therapy** for the treatment of non-insulin dependent
                        diabetes mellitus (Review).
AUTHOR: Freeman D J; Leclerc I; Rutter G A
CORPORATE SOURCE: Department of Biochemistry, School of Medical Sciences,
                        University Walk, University of Bristol, Bristol BS8 1TD,
                        UK.
AB   This review describes the latest approaches towards using **gene
     therapy** as a treatment for non-insulin dependent **diabetes**
     mellitus (NIDDM; Type 2 **diabetes**). We examine attempts to
     directly deliver the **insulin gene** to non-beta-cells,
     to improve insulin secretion from existing beta-cells and to develop ex
     vivo approaches to implanting genetically modified cells. Future research
     into the pathology of non-insulin dependent **diabetes**, combined
     with the latest developments in gene delivery systems, may potentially
     make **gene therapy** an attractive alternative NIDDM
     treatment in the future.